Gender Differences of Thromboembolic Events in Atrial Fibrillation

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Atrial fibrillation (AF) is the most common clinically relevant arrhythmia and increases the risk of thromboembolism and stroke; however, these risks are not the same for women and men. This review examines the evidence and clinical significance of increased thromboembolic risk in women with AF. The balance of results from over 30 recent studies suggests that female gender is an independent stroke risk factor in AF, and the inclusion of female gender in stroke risk stratification models, such as CHA_2DS_2-VASc, has improved risk assessment. Reasons for the increased thrombogenicity in women remain incompletely elucidated, but biological factors including increased hypertension, renal dysfunction, and hyperthyroidism in female patients with AF; cardiovascular remodeling; increased hypercoagulability, and estrogen hormone replacement therapy in women have been proposed. More importantly, gender differences exist in medical management of patients with AF, and compared with men, women have been found to have greater thromboembolic risk when not on anticoagulants, but may benefit from greater risk reduction when systemically anticoagulated. In conclusion, increased clinician awareness of these gender differences may help to improve the management of patients with AF. **(Am J Cardiol 2016;117:1021−1027)**

Atrial fibrillation (AF), the most common clinically relevant arrhythmia, affects 2.7 to 6.1 million Americans, with prevalence projected to double by the year 2050.[1] The prevalence of AF is 3.2% of the population aged ≥20 years and reaches 20% at age 80.[2] Men have a greater risk of developing AF than women by a factor of 1.5 after adjusting for other risk factors.[3] However, the absolute numbers of men and women with AF are roughly equal because of the higher average life expectancy of women.[4,5] Women make up about 60% of the population with AF aged >75, the median age of AF onset.[6]

AF is associated with a fivefold increased risk of stroke[7] and is attributed with at least 50% of strokes occurring in subjects aged 80 years and older.[2] Many risk stratification models have been proposed to quantify the risk of stroke in AF. The inclusion of female gender as an independent risk factor has been the subject of recent examination. AF is more frequently noted in women presenting with stroke than in men.[8] In addition, women have a worse poststroke outcome than men in terms of motor and cognitive function and activities of daily living.[9] AF is an independent stroke predictor of in-hospital mortality for women but is not for men.[10]

Thus, these gender differences are clinically relevant to make accurate estimations of inherent stroke risk in patients with AF. This is important because patients with AF with the highest stroke risk derive the greatest absolute benefit from systemic anticoagulation.[11] As such, clinician awareness of such gender differences becomes useful when a decision regarding anticoagulation is needed and few or no other risk factors exist. Current European Society of Cardiology (ESC) guidelines recommend that no systemic anticoagulation is required for female patients aged <65 years with lone AF (CHA_2DS_2-VASc = 1) because these patients are considered low risk for stroke, which stands in contrast to other subgroups with CHA_2DS_2-VASc = 1. The primary objective of this review is to provide an updated overview of the existing evidence for gender differences in thromboembolic risk and to discuss the clinical importance of such differences.

Methods

The PubMed database was used to review the English language reports addressing gender differences and thromboembolic risk in AF from 1994 to the present. The search used combinations of terms including "atrial fibrillation," "gender OR sex OR female OR women," and "thromboembolism OR stroke." References of retrieved studies were further reviewed in detail for additional relevant studies and reviews.

Studies were selected for inclusion if they published stroke incidence data in men and in women. The number of women, number of total study participants, mean age of men and women, percent incidence of stroke in men and women, and relative risk (RR) for stroke for women were collected from each study when available. Difference in stroke risk was evaluated by examining the reported RR values, and if these were unavailable, by examining the *p*-value for statistically significant differences in stroke rates between men and women.

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Evidence for Gender Differences in Thromboembolic Risk: We compiled over 30 studies published since 1999 that examine gender and thromboembolic risk, including 5 randomized controlled trials (RCTs) and 24 observational studies (Tables 1 and 2). Of these 30 studies, 17 studies reported that female gender is a significant risk factor,[13–16,19,21,22,25,27,31,33–39] 12 studies reported that female gender is not significant,[17,18,20,23,24,26,28–30,32,40,41] and only 1 study reported that male gender is a significant risk factor.[12] Four additional RCTs compared novel oral anticoagulant drugs (NOAC) and warfarin, providing further data on gender differences (Table 3).[42–45] However, 1 RCT[37] and 1 observational study[34] no longer found a significant difference after multivariate analysis. Four studies, all reporting insignificant gender differences, only reported univariate risk estimates associated with female gender.[18,24,29,32]

Although only 13 of the 25 observational studies reported female gender as significant, 2 of the 12 observational studies that reported no significant gender differences had abnormal age distributions, which may have skewed the data. The Elderly Patients followed by Italian Centres for Anticoagulation (EPICA) study only included patients over 80 years old,[13] and a Beijing hospital study reported that the lack of significant gender differences may be because the female patients were younger and had fewer co-morbidities.[19]

The Stroke Prevention in Atrial Fibrillation (SPAF) trials of the 1990s provided early data on gender differences.[38] These studies reported that women with AF have a greater risk of stroke than men (RR 1.6, $p = 0.01$), and this difference in stroke rate was substantially greater in patients aged >75 years. The largest RCT was the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study with a cohort of 13,559 adults with AF.[36] This was the first RCT with enough end points to examine the influence of gender on stroke risk. The study reported that the annual incidence rates of thromboembolism off warfarin were 3.5% for women versus 1.8% for men (RR 1.9, 95% CI 1.6 to 2.4). The difference between the RR of thromboembolism for women versus men for those aged ≤75 years (RR 1.6, 95% CI 1.0 to 2.3) and those aged >75 years (RR 1.8, 95% CI 1.4 to 2.3) was not statistically different.

Gender as an Independent Stroke Risk Factor: Interestingly, the balance of evidence suggests that female gender is an independent thromboembolic risk factor. Several meta-analyses have also found that women appear to have an increased stroke risk compared with their male counterparts. One meta-analysis of 17 studies reported a 1.31-fold (95% CI 1.18 to 1.46) increased stroke risk in women with AF, especially those aged ≥75 years, regardless of oral anticoagulation (OAC) therapy.[46] Another meta-analysis reported that women with AF have a significantly greater residual risk of cerebrovascular accident/systemic embolism compared with men with AF (odds ratio 1.279, 95% CI 1.111 to 1.473, $p = 0.001$) while on warfarin, but there was no significant gender difference in residual risk of cerebrovascular accident/systemic embolism in patients with AF on novel OACs (odds ratio 1.146, 95% CI 0.97 to 1.354, $p = 0.109$).[47] A meta-analysis analyzing the warfarin arm of 6 studies found that women with AF treated with OAC therapy still had higher stroke rates than men (RR 1.30, 95% CI 1.15 to 1.49, $p < 0.001$).[48] Likewise, there have been several systematic reviews of contemporary data on stroke in women with AF that have found female gender to be an independent predictor of stroke in AF with reported average RRs of 1.5 to 1.9.[49–51]

Comparison of Stroke Risk Stratification Models Regarding Gender: Female gender is increasingly recognized as a stroke risk factor in AF (Table 4). A previously commonly used stroke risk stratification model, $CHADS_2$ (1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points for previous stroke/transient ischemic attack) does not include gender.[52] A large Swedish cohort study found that at each $CHADS_2$ score, the stroke rate was higher in women than in men.[22] In light of the mounting evidence suggesting increased thromboembolic risk in women compared with men, the CHA_2DS_2-VASc (CHA_2DS_2 and 1 point each for vascular disease, age 65 to 74 years, and gender category) model was developed to complement $CHADS_2$ by considering additional stroke risk factors, including female gender, age 65 to 74, and vascular disease.

Several studies support the use of CHA_2DS_2-VASc score, particularly for its additional predictive value for patients with low $CHADS_2$ scores.[31,53] A Danish cohort study reported that CHA_2DS_2-VASc performed better than $CHADS_2$ in identifying patients at high risk and at truly low risk.[19] Likewise, a Chinese AF cohort study found that the 3 new components of CHA_2DS_2-VASc, including age 65 to 74 years, female gender, and a history of other vascular disease, were predictive of stroke in their cohort.[34] A study on postmenopausal women with AF found that for $CHADS_2$ <2, stroke risk almost doubles with each additional CHA_2DS_2-VASc point.[54] A Taiwanese study reported that women with AF with a CHA_2DS_2-VASc score of 1 (no risk factors other than gender) had a 2.5-fold stroke risk compared with men with AF with a score of 0, further validating the additional point for female gender.[21]

That women with AF are at higher risk for thromboembolic events has been highlighted by the recognition and inclusion of female gender as an independent risk factor in newer stroke risk prediction models. However, although there are data to suggest that women with AF are more likely to suffer a thromboembolic event and tend to suffer worse clinical outcomes poststroke than their male counterparts, it has been noted that the more recent the study of excess female risk for thromboembolic events in AF, the lower this risk appears to be. In the 2003 Framingham study,[13] the risk for women was increased by 90%; by 80% in the 2007 Euro Heart Survey[15]; by 50% in the 2005 ATRIA study[36]; and by 47% in the large Swedish cohort study[22] in 2012. This is reflected in the 2012 ESC guidelines stating that women aged <65 years with lone AF are considered low risk and thus, no antithrombotic therapy should be considered. A female patient with AF can have 0 or 2 to 9 points with the CHA_2DS_2-VASc scoring system, as female gender is currently only recognized as a risk factor in the presence of at least one other risk factor.

Reasons Why Stroke Risk in Women May Be Increased: Many reasons have been hypothesized to account for the apparent increased thrombogenicity in women

Table 1
Observational studies addressing gender

Publication (year)	Cohort	Total n	# of females	% female	Age (years)			Stroke (%)			Relative Risk	
					Males	Females	*p* Value	Males	Females	*p* Value	Females	*p* Value
Inoue (2000)[12]*	Japan	740	234	31.6	56 †		NR	NR	NR	NR	RR 0.5 M	0.0291
Humphries (2001)[5]*	CARAF (Canada)	1097	339	30.9	60.5±0.6	65.4±0.7	<0.001	6.5‡	7.8‡	NS	NR	NR
Wang (2003)[13]	Framingham Heart Study (USA)	705	336	47.7	75 †		NR	NR	NR	NR	HR 1.92 M	NR
Friberg (2004)[14]	Copenhagen City Heart Study	276	110	39.9	67±8.4	69±6.8	NR	7.8	20	NR	HR 2.6 M	NR
								4.7 years§				
Dagres (2007)[15]*	Euro Heart Survey on AF	5333	2249	42.2	64±13	70±12	<0.001	1.2	2.2	0.011	OR 1.83 M	0.019 M
								1 year§				
Poli (2009)[16]*	University of Florence (Italy)	780	275	35.3	74	76	<0.001	1.2¶	2.43¶	0.042	HR 2.3 M	<0.01
Ruigomez (2009)[17]*	UK General Practice Research	831	426	51.3	61.2% subjects aged ≥70†		NR	NR	NR	NR	RR 1.0 M	NS
Lin (2011)[18]	Taiwan NHI research database	7920	3633	45.9	63.3% subjects aged ≥65†		NR	NR	NR	NR	OR 0.942 U	0.512 U
Oleson (2011)[19]	Denmark national register	73538	37651	51.2	59.7% subjects aged ≥75†		NR	NR	NR	NR	HR 1.6 M	0.04 M
van Staa (2011)[20]	United Kingdom	79844	39704	49.7	73.3 †		NR	1.2	1.9	NR	RR 1.05 M	NS
								4 years§				
Chao (2012)[21]*	Taiwan NHI research database	829	320	38.6	45.4 ± 12 †		1	1.6	4.4	0.014	HR 2.48 M	0.042 M
								57.4 ± 35.7 months§				
Friberg (2012)[22]	Sweden	100802	50667	50.3	74.7	80.9	NR	4.2‖	6.2‖	<0.0001	HR 1.47 U; 1.18 M	<0.001
Mikkelsen (2012)[23]	Denmark	87202	44744	51.3	71	78.2	<0.0001	3.7¶	5.43¶	NR	HR 1.04 M	NR
Potpara (2012)[24]	Belgrade AF Study (Serbia)	862	315	46.5	49.6	56.7	<0.001	6.9	7	0.579	HR 1.11 U	0.579 U
								10.1±6.1 years§				
Tsadok (2012)[25]*	Quebec (Canada)	83513	44115	52.8	77.2	80.2	NR	4.3	5.8	<0.001	HR 1.14 M	<0.001 M
								30, 90, 365 days§				
Bosch (2013)[26]*	Germany	2742	1021	37.2	67.5±9.9	71.2±9.3	<0.001	3.4	3.6	0.74	NR	NR
								6, 12 months§				
Disertori (2013)[27]*	GISSI-AF subset	1234	487	39.5	66.75 paroxysmal AF; 68.78 persistent AF†		NR	3	9	NR	NR	NR
								1 year§				
Guo (2013)[28]	Chinese PLA General Hospital	1034	281	27.2	78	71	<0.0001	8.1	6.05	0.267	NR	NR
								1.9 years§				
Poli (2013)[29]*	EPICA study (Italy)	3015	1654	54.9	82.6**	83.1**	0.001	1.3¶§	1.6¶	0.25	OR 1.2 U	0.3 U
Salam (2013)[30]*	Hamad General Hospital (Qatar)	3849	1417	36.8	54.5 ± 15.7	59 ± 15	0.001	0.4	0.4	0.8	NR	NR
								20 years§				
Aakre (2014)[31]	Olmsted County, Minnesota (USA)	2720	1320	48.5	73.33±14.57 †		NR	NR	NR	NR	HR 1.45 M	0.0015 M
Inoue (2014)[32]	J-RHYTHM	7406	2165	29.2	69±10	73±9	<0.001	1.8	1.6	0.576	OR 0.89 U	0.576 U
								2 years§				

(*continued*)

Table 1
(*continued*)

Publication (year)	Cohort	Total n	# of females	% female	Age (years)			Stroke (%)			Relative Risk		
					Males	Females	*p* Value	Males	Females	*p* Value	Females	*p* Value
Shroff (2014)[33]	US Medicare patients 2010	80314	40879	50.9	NR	NR	NR	1.4‡	1.9‡	NR	NR	NR
Siu (2014)[34]	Queen Mary Hospital, Hong Kong	9727	5064	52.1	76.9±12.5 †		NR	NR	NR	NR	HR 1.16 U; 1.03 M	0.026 U; 0.723 M
Yang (2014)[35]*	Chinese AF registry	2016	1104	54.8	68.5		NR	NR	NR	NR	HR 1.359 U; 1.419 M	0.073 U; 0.048 M

GISSI-AF = Gruppo Italiano Studio Sopravvivenza Insufficienza; HR = hazard ratio; J-RHYTHM = Japanese Rhythm Management Trial for AF; M = multivariate analysis; NHI = National Health Insurance; OR = odds ratio; PLA = People's Liberation Army; RR = relative risk; U = univariate analysis.

* Study does not explicitly state whether patients with valvular AF were excluded. All unmarked studies recruited patients with nonvalvular AF.

† Gender-specific mean age not provided.

‡ Estimated from figure.

§ Mean follow-up duration provided for studies with stroke percentage incidence reported during study follow-up.

¶ Events/100 patient-years.

‖ Percent per year.

** Median age.

with AF. Differences in baseline patient characteristics involving AF presentation, medical co-morbidities, and stroke risk profiles may contribute to the increased stroke risk in women.[55] Age is a well-known risk factor for stroke, and female patients in most studies were older, in the large Swedish cohort study, the mean age was 6 years higher in women than men,[22] and it has been argued that this could account for the increase in thromboembolic risk. One study reported significantly larger left atrial dimensions in women (44.0 ± 6.5 vs 40.6 ± 6.3, $p = 0.0026$); however, another study found no difference in atrial size.[16] Women with AF are also more likely to have preexisting hypertension,[5,15,22,25,37,41] valvular heart disease,[3,15] and heart failure with preserved left ventricular function,[15] but less likely to have coronary artery disease than men.[15,36] Women are more likely to have preexisting thyroid abnormalities,[15,49] which may also contribute to their increased thromboembolic risk. A 2010 study found that hyperthyroidism contributed a 1.44-time greater risk of ischemic stroke (95% CI 1.01 to 2.12; $p = 0.038$), after adjusting for age, gender, and AF, among other factors.[56] In addition to these co-morbidities, in particular, women with AF are more likely than their male counterparts to have a history of previous stroke—the strongest independent predictor for stroke.[22,25,36] However, many of the larger cohort studies adjusted for these co-morbidities and yet still found that women have a higher stroke risk.[46]

Other reasons suggested for the increased stroke risk in women include the possibility that women may have increased hypercoagulable qualities, such as endothelial dysfunction and prothrombotic factors, including elevated fibrinogen levels,[57] von Willebrand factor,[58,59] and increased platelet activation.[55,60,61] In addition, hormone replacement therapy (HRT) has been posited as a potential reason for the difference in thrombogenicity. SPAF III reported that estrogen hormone replacement therapy was independently associated with significantly higher rates of ischemic stroke in women with AF,[38] whereas ATRIA and the Stroke Prevention using an Oral Thrombin Inhibitor (SPORTIF) study did not find a significant association.[36,37] However, the mixed evidence and low percentages of women using estrogen HRT in these studies suggest that this may not be the sole factor for increased stroke risk.

Clinical Relevance of Gender Differences in Thromboembolic Risk: Compared with men, women tend to be more symptomatic—experiencing longer episodes, more frequent recurrences, and faster ventricular response rates during AF.[5,6,41,49,62] Women with AF also tend to have lower quality of life[15,41,62,63] and are older than men at the time of presentation.[5,9,15,25,30,37,41,64,65] In addition to these clinical differences in presentation between men and women with AF, there are also disparities in the medical management of these patients. These gender differences in the medical management of AF may increase stroke risk differences in men and women. In patients with atypical or no AF symptoms in the Euro Heart Survey on Atrial Fibrillation, treatment was more conservative in women, with significantly less utilization of rhythm-control strategies than in men.[15] In a Serbian study, men were more likely to undergo electrocardioversion or to be prescribed

Table 2
Randomized controlled trials (RCTs) addressing gender

Publication (year)	Cohort	Total n	# of females	% female	Age (years)			Stroke (%)			Relative Risk	
					Males	Females	*p* Value	Males	Females	*p* Value	Females	*p* Value
Hart (1999)[38]	SPAF I-III	1853	514	27.7	68	71	NR	2.1*	4.4*	NR	RR 1.8 U; 1.6 M	0.03 U; 0.01 M
Fang (2005)[36]	ATRIA cohort	13559	5795	42.7	NR	NR	NR	1.8*	3.5*	NR	RR 1.6 M	NR
Rienstra (2005)[41] †	RACE substudy	522	192	36.8	67±9	71±8	<0.001	6.7	6.8	NS	NR	NR
									2.3 years‡			
Gomberg-Maitland (2006)[37]	SPORTIF III and V	7329	2257	30.8	69.8±9	73.4±8	<0.0001	1.44*	2.08*	0.016	HR 1.44	0.0161
											U; 1.27 M	U; 0.16 M
Sullivan (2012)[39]	AFFIRM substudy	4060	1594	39.3	68.3±8.3	71.3±7.5	<0.0001	3	5	0.002	OR 1.6 M	0.002 M
									2000 days‡			

All studies recruited patients with nonvalvular AF.
AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; HR = hazard ratio; M = multivariate analysis; OR = odds ratio; RR = relative risk; U = univariate analysis.
* Percentage per year.
† Additional therapies examined calcium channel blockers, β blockers, electrocardioversions, antiarrhythmic drugs.
‡ Mean follow-up duration provided for studies with stroke percentage incidence reported during study follow-up.

Table 3
NOAC drug studies addressing gender

Publication (year)	Cohort	Arm of Study	Total n	# of females	% female	Age (years)			Stroke (%)		
						Males	Females	*p* Value	Males	Females	*p* Value
Connolly (2009)[42]	RE-LY	Dabigatran 110 mg	6015	2150	35.7	71.4±8.6	*	NR	1.35†	1.86†	0.96
		Dabigatran 150 mg	6076	2236	36.8	71.5±8.8	*	NR	1.10†	1.14†	0.24
		Warfarin	6022	2213	36.7	71.6±8.6	*	NR	1.49†	2.03†	NR
Connolly (2011)[43]	AVERROES	Apixaban	2808	1148	40.9	68.6	71.4	NR	1.4†	1.9†	0.42
		Aspirin	2791	1174	42.1	68.8	71.8	NR	2.7†	4.9†	0.42
Granger (2011)[44]	ARISTOTLE	Apixaban	9120	3234	35.5	70‡	*	NR	1.2†	1.4†	0.6
		Warfarin	9081	3182	35	70‡	*	NR	1.5†	1.8†	0.6
Patel (2011)[45]	ROCKET-AF	Rivaroxaban	7131	2831	39.7	73‡	*	NR	NR	NR	NR
		Warfarin	7133	2832	39.7	73‡	*	NR	2.02§	2.67§	<0.001

All studies recruited patients with nonvalvular AF.
ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF; AVERROES = Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF.
* Gender-specific mean age not provided.
† P per year.
‡ Median age.
§ Events/100 patient-years.

OAC (both $p < 0.001$), whereas women were more likely to be prescribed β blockers and calcium channel blockers (both $p < 0.01$).[24]

Similarly, a recent study in France found that women over the age of 75 years were 1/3 less likely to be treated with systemic anticoagulation than men of similar age.[66] The Canadian Registry of Atrial Fibrillation (CARAF) study found that older women were half as likely to receive warfarin and twice as likely to receive aspirin compared with older men.[5] When women are prescribed systemic anticoagulation, differences may also exist in terms of the quality of anticoagulation. According to the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, women with AF on warfarin spent less time in therapeutic range (TTR) than men ($40 \pm 0.7\%$ vs $37 \pm 0.5\%$, $p = 0.0001$), with more time spent below TTR ($29 \pm 0.7\%$ vs $26 \pm 0.5\%$, $p = 0.0002$).[39] Differences in TTR, an important predictor of thromboembolic outcomes in AF, could indicate lower quality of warfarin anticoagulation in females.

The lower rates of anticoagulation prescription for female patients may be related to the perception of increased bleeding risk in women compared with men. The CARAF study reported a 3.35-fold increased risk of major bleeding in women on warfarin compared with men on warfarin.[5] The SPORTIF trials found no difference in major bleeding rates ($p = 0.766$), but women experienced more overall bleeding ($p < 0.001$) and were more prone to anticoagulant-related bleeding.[37] However, they also reported that the higher rate of thromboembolism in women was related to more frequent interruption of anticoagulant therapy. The ATRIA study found that the

Table 4
Recent evolution of risk stratification models

Year	Risk Stratification Model	Gender as Risk Factor
2001	$CHADS_2$	Female gender not included
2003	Framingham stroke risk score	Female gender incorporated as risk factor
2006	ACC/AHA/ESC guidelines	Recognized female gender as one of the "less validated or weaker risk factors"
2009	CHA_2DS_2-VASc	Female gender incorporated as risk factor
2010/2012	ESC guidelines	Upgraded female gender from a "less validated or weaker risk factor" to a "clinically relevant non-major risk factor"
2012	Canadian Cardiovascular Society guidelines update	Recommended use of $CHADS_2$ in 2010. In 2012, guidelines updated to consider CHA_2DS_2-VASc if $CHADS_2 = 0$ and addressed single point for female

ACC/AHA/ESC = American College of Cardiology/American Heart Association/European Society of Cardiology.

reduction in rates of thromboembolism with warfarin was larger in women than in men ($p = 0.01$ for interaction of gender and warfarin) and found no gender differences in rates of major hemorrhage while on warfarin.[36] The Rate Control versus Electrical Cardioversion (RACE) study reported a lower incidence of bleeding in women compared with men.[41] SPAF reported that women derived greater benefit from anticoagulation than did men.[67] Thus, these gender differences become important because although women may derive more benefit from systemic anticoagulation than their male counterparts, they may be less likely to receive systemic anticoagulation and when they are anticoagulated, the quality of anticoagulation may be lower.

Disclosures

The authors have no conflicts of interest to disclose.

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